

ABCA1 STABILIZER

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FIELD OF THE INVENTION

The present invention relates to an ATP-binding cassette transport 1 (ABCA1) stabilizer. The ABCA1 stabilizer comprises, as an effective ingredient, a bisphenol-type compound selected from probucol spiroquinone (chemical name: 2,4,9,11-tetrakis(1,1-dimethylethyl)-14,14-dimethyl-13,15-dithiadispiro[5.0.5.3]pentadeca-1,4,8,11-tetraene-3,10-dione), probucol diphenoxinone (chemical name: 3,5,3',5'-tetra-t-butyl-4,4'-diphenoxinone), and probucol bisphenol (chemical name: 4,4'-dihydroxy-3,5,3',5'-tetra-t-butyldiphenyl). These bisphenol compounds are metabolites of probucol. The present invention further relates to a prophylactic/therapeutic agent comprising at least one ABCA1 stabilizer. The prophylactic/therapeutic agent is used for treating various diseases caused by a decrease in the ABCA1 expression, such as low-HDL (high-density lipoprotein) cholesterolemia and arteriosclerosis. Here, the ATP is an abbreviation for adenosine 5'-triphosphate that is involved in energy metabolism in vivo and plays an important role in acquisition and utilization of energy.

BACKGROUND OF THE INVENTION

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Probucol is a compound having the chemical name 4,4'-(isopropylidenedithio)bis(2,6-di-t-butylphenol). Main functions of probucol are said to promote catabolism of cholesterol and its excretion into bile. Furthermore, probucol raises the catabolism rate of low-density lipoprotein (LDL)-cholesterol and reduces the serum total cholesterol level. Consequently, probucol is widely used

as an agent for improving lipid metabolism in hyperlipidemia patients (including familial hypercholesterolemia and xanthoma patients).

However, probucol also has a clinically 5 disadvantageous effect, i.e., reduces the cholesterol level in the HDL fraction (hereinafter sometimes referred to as "HDL-cholesterol"), unlike other lipid-lowering agents which have the reaction properties in LDL such as statins or fibrates (for example, refer to Non-Patent Documents 1 10 and 2). As the statin lipid-lowering agents, pravastatin and simvastatin known as HMG-CoA reductase inhibitors are known. As the fibrate lipid-lowering agents, fenofibrate and bezafibrate are known. It is thought that this reduction in HDL-cholesterol is due to functional 15 inhibition of ABCA1 (for example, refer to Non-Patent Documents 3, 4, and 5).

It is known that probucol spiroquinone, probucol diphenoquinone, and probucol bisphenol according to the present invention are produced as metabolites when probucol 20 is orally administered to a mammal (for example, prefer to Non-Patent Document 6).

Some pharmacological activities of probucol spiroquinone, probucol diphenoquinone, and probucol bisphenol (hereinafter sometimes preferred to as 25 "bisphenol-type compounds", or collectively the "bisphenol-type compound") are known at present. For example, it is disclosed that probucol bisphenol has antioxidant properties and is used in combination with probucol as a lipoprotein oxidation inhibitor (for example, refer to Patent Document 1). In addition, it is known that the 30 bisphenol-type compounds incorporate cholesterol into cells (for example, refer to Non-Patent Document 7). However, in these prior findings, functions of the bisphenol-type compounds on ABCA1 and HDL are not disclosed at all.

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HDL is a lipid/protein complex particle produced by the action of helix-like apolipoproteins such as

apoprotein A-I (hereinafter sometimes referred to as "apoAI") mainly synthesized in and secreted from liver cells and small-intestine epithelial cells and the ABCA1 protein present in cell membranes. Immediately after
5 secretion, HDL is formed as a discoidal particle composed of major constituents, apoAI and phospholipid, and called nascent HDL. This nascent HDL receives, in blood, free cholesterol from cell membranes of peripheral cells or surfaces of other lipoproteins, and forms mature spherical
10 HDL while holding, at its hydrophobic center, cholesterol ester converted from the cholesterol by the action of LCAT (lecithin cholesterol acyltransferase).

In the above-mentioned process, HDL plays a major role in extremely important physiological function in terms
15 of lipid metabolism called "cholesterol reverse-transport system" which takes, in blood, excessive cholesterol out of peripheral tissues and transports it to the liver. The cholesterol reverse-transport system is considered to work for removing cholesterol accumulated in blood vessel wall
20 cells and to cause a prophylactic action on arteriosclerosis.

With respect to a relationship between blood levels of HDL cholesterol and arteriosclerosis, many epidemiological studies have been conducted. As a result,
25 it has been recently revealed a fact that lower HDL cholesterol levels result in a higher incidence of arteriosclerosis. The improvement of low HDL-cholesterolemia is a more important and novel technology as prophylactic/therapeutic treatment of arteriosclerosis,
30 compared to a therapy using the statins or fibrates widely used at present for reducing LDL.

At present, the blood level of HDL is determined by referring to the level of HDL-cholesterol. In general, when the blood HDL cholesterol level of a subject is lower
35 than 40 mg/dl, the subject is diagnosed as "low-HDL cholesterolemia".

Low-HDL cholesterolemia is found as a risk factor

at a high incidence in not only arteriosclerosis but also
in various disorders such as hyperlipidemia, myocardial
infarction, cerebral infarction, cerebral apoplexy, obesity,
diabetes mellitus, and nerve disorders caused by diabetes
5 mellitus. Low-HDL cholesterolemia is also caused by
various genetic diseases including Tangier disease.
However, a useful prophylactic/therapeutic agent that acts
on HDL itself has been desired to be developed. Such a
prophylactic/therapeutic agent for treatment of low-HDL
10 cholesterolemia has not been found yet.

In order to treat low-HDL cholesterolemia, a
number of trials for increasing HDL have been conducted.
As a result of such trials, pharmacological effects of
ABCA1 have been identified.

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ABCA1 is a protein mainly present in cell
membranes of various organs such as the liver, small
intestine, placenta, and adrenal gland, and belongs to the
ABC protein family that is considered to be involved in
20 membrane transport of various substances such as lipids,
amino acids, vitamins, and saccharides (for example, refer
to Non-Patent Document 8).

A recent finding revealed that ABCA1 was a
protein indispensable for a reaction generating HDL from
25 lipids in cells and a rate-limiting factor of HDL
production. In addition, it was revealed that the HDL
formation by ABCA1 is a main removing pathway of cellular
cholesterol.

For example, in patients with Tangier disease
30 whose ABCA1 gene has a mutation and who are deficient in
expressing ABCA1, plasma HDL almost disappears (for example,
refer to Non-Patent Documents 9, 10, and 11). In addition,
it was found that incorporation of ABCA1 gene accelerates a
HDL-generating reaction (for example, referred to Non-
35 Patent Documents 12 and 13). Several trials are now in
progress to elevate or regulate HDL cholesterol levels by
increasing the ABCA1 expression level in vivo with genetic

engineering technology.

For example, for increasing cholesterol efflux and HDL levels, the expression level and activity of ABCA1 are elevated by direct gene transfer of an ABCA1-coding gene into a host cell (for example, refer to Patent Documents 2 and 3). The expression and activity of ABCA1 are increased by using a certain substance to facilitate the transcription and translation of the ABCA1 gene for controlling the levels of HDL cholesterol and triglyceride (for example, refer to Patent Document 4). Furthermore, for controlling the cholesterol efflux to the outside of cells, the expression of ABCA1 is increased by activating peroxisome proliferator activated receptor- α (PPAR- α) or peroxisome proliferator activated receptor- δ (PPAR- δ) having various activities as an intranuclear receptor (for example, refer to Patent Document 5).

However, in the above-mentioned known technologies focused on ABCA1 and HDL, a genetic engineering technology or a method for activating an intranuclear receptor is used. Therefore, there are disadvantages such that the technology for a genetic therapy is immature and that a risk of unexpected side effects caused by activating an unknown gene is not ignorable. Thus, the use as a drug has not been accomplished yet.

[Patent Document 1] International Publication WO 02/04031

[Patent Document 2] International Publication WO 00/78971

[Patent Document 3] International Publication WO 00/78972

[Patent Document 4] International Publication WO 01/15676

[Patent Document 5] Japanese Unexamined Patent Application Publication No. 2003-12551

[Non-Patent Document 1] CIRCULATION, (US), 79, 1989, 16-28

[Non-Patent Document 2] JOURNAL of CARDIOVASCULAR

PHARMACOLOGY, (US), 30, 1997, 784-789

[Non-Patent Document 3] BIOCHEMISTRY, (US), 35(40), 1996,
13011-13020

【Non-Patent Document 4】 BIOCHIMICA et BIOPHYSICA ACTA, (Netherlands), 1483, 2000, 199-213

【Non-Patent Document 5】 Arteriosclerosis, thrombosis, and vascular biology, (US), 21, 2001, 394-400

5 【Non-Patent Document 6】 ANALYTICAL CHEMISTRY SYMPOSIA SERIES, (US), 7, 1981, 35-38

【Non-Patent Document 7】 LIPIDS, (US), 29(12), 1994, 819-823

10 【Non-Patent Document 8】 ANNUAL REVIEW of CELL BIOLOGY, (US), 8, 1992, 67-113

【Non-Patent Document 9】 NATURE GENETICS, (US), 22, 1999, 336-345

【Non-Patent Document 10】 NATURE GENETICS, (US), 22, 1999, 347-351

15 【Non-Patent Document 11】 NATURE GENETICS, (US), 22, 1999, 352-355

【Non-Patent Document 12】 THE JOURNAL of CLINICAL INVESTIGATION, (US), 104, 1999, R25-R31

【Non-Patent Document 13】 THE FASEB JOURNAL, (US), 15, 2001, 20 1555-1561

SUMMARY OF THE INVENTION

25 As described above, low-HDL cholesterolemia is often observed in hyperlipidemia, obesity, and diabetes mellitus and is a serious risk factor of arterioscleroses such as myocardial infarction, cerebral infarction, and cerebral apoplexy. The present invention provides a 30 prophylactic/therapeutic agent for various diseases such as arteriosclerosis based on mechanisms wherein ABCA1 is stabilized with a specific bisphenol-type compound, thereby resulting in elevating ABCA1 levels followed by an increase in production of HDL.

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The present inventors have studied for various materials in order to overcome the above-mentioned

disadvantages in the conventional method and to find an agent affecting an HDL-generating mechanism and being useful as a prophylactic/therapeutic agent for low-HDL cholesterolemia. As a result, the inventors have found a prophylactic/therapeutic agent for low-HDL cholesterolemia and filed a patent application already published as WO 03/033023 A1. The agent contains an effective amount of a cysteine-protease inhibitor which suppresses or inhibits the degradation of ABCA1, thereby resulting in elevated ABCA1 levels.

The present inventors have further conducted extensive studies and succeeded in finding that the aforementioned bisphenol-type compounds have actions of suppressing or inhibiting the degradation of ABCA1 to cause the continuous and stable expression of ABCA1, thereby leading to elevated HDL levels. Thus, the present invention has been provided. The HDL level-elevating action of the bisphenol-type compounds is quite contrary to the function of probucol which has been hitherto known to decrease the HDL level relying on inhibition of the ABCA1 function. Hence, the present invention is not predictable at all from the above-mentioned known technologies. Thus, the present invention provides an agent which overcomes the defect of probucol.

The present invention provides an ABCA1 stabilizer comprising an effective amount of a bisphenol-type compound selected from probucol spiroquinone, probucol diphenoquinone, probucol bisphenol, and salts thereof (hereinafter sometimes simply preferred to as "the bisphenol-type compounds" or "said bisphenol-type compounds"); a prophylactic/therapeutic agent for low-HDL cholesterolemia, which comprises an effective amount of said ABCA1 stabilizer; a prophylactic/therapeutic agent for arteriosclerosis, which comprises an effective amount of said ABCA1 stabilizer; and a drug comprising an effective

amount of at least one member selected from the group consisting of said ABCA1 stabilizer, said prophylactic/therapeutic agent for low-HDL cholesterolemia, and said prophylactic/therapeutic agent for
5 arteriosclerosis, in combination with an effective amount of at least one drug selected from the group consisting of antidiabetes drugs, therapeutic drugs for complications of diabetes, antiobesity drugs, antihypertensive drugs, antihyperlipidemic drugs, diuretics, antithrombotic drugs,
10 and anti-Alzheimer drugs.

The present invention further provides an agent for 1) elevating the in vivo level of ABCA1 and accelerating in vivo HDL-generating reaction, 2) elevating
15 the blood level of HDL, 3) increasing the activity of the blood cholesterol reverse transport that removes cholesterol from peripheral tissues, and/or 4) suppressing or inhibiting the degradation of ABCA1 and accelerating the HDL-generating reaction in vivo, which comprises an
20 effective amount of said bisphenol-type compounds. The present invention further provides a prophylactic/therapeutic agent for low-HDL cholesterolemia, which comprises an effective amount of said agent according to any of the above 1) to 4); a prophylactic/therapeutic
25 agent for arteriosclerosis, which comprises an effective amount of said agent according to any of the above 1) to 4); and a drug comprising an effective amount of at least one agent according to any of the above 1) to 4), in combination with an effective amount of at least one drug
30 selected from the group consisting of antidiabetes drugs, therapeutic drugs for complications of diabetes, antiobesity drugs, antihypertensive drugs, antihyperlipidemic drugs, diuretics, antithrombotic drugs, and anti-Alzheimer drugs.

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The present invention further provides A) a method for a) stabilizing ABCA1, b) increasing the ABCA1

level and accelerating the HDL-generating reaction in vivo,
c) increasing the blood level of HDL, d) increasing
activity of the blood cholesterol reverse-transport system
which removes cholesterol from peripheral tissues, and/or
5 e) suppressing the degradation of ABCA1 and accelerating
the HDL-generating reaction in vivo, which comprises
administering an effective dose of the bisphenol-type
compounds to a subject (or patient). The present invention
further provides B) a method for prophylactic/therapeutic
10 treatment of low-HDL cholesterolemia which comprises
administering an effective dose of any one of the above-
mentioned agents to a subject; C) a method for
prophylactic/therapeutic treatment of arteriosclerosis,
which comprises administering an effective dose of any one
15 of the above-mentioned agents to a subject (or patient);
and D) a method for prophylactic/therapeutic treatment of a
disease, which comprises administering an effective dose of
any one of the above-mentioned agents, in combination with
an effective dose of at least one drug selected from the
20 group consisting of antidiabetes drugs, therapeutic drugs
for complications of diabetes, antiobesity drugs,
antihypertensive drugs, antihyperlipidemic drugs, diuretics,
antithrombotic drugs, and anti-Alzheimer drugs.

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ADVANTAGEOUS PROFILES OF THE INVENTION

The ABCA1 stabilizer according to the present
invention, which contains, as an effective ingredient, a
30 bisphenol-type compound selected from probucol spiroquinone,
probucol diphenoxquinone, probucol bisphenol, and salts
thereof, facilitates, free of requiring genetic engineering
techniques, continuous and stable ABCA1 expression with a
mechanism completely different from the conventional
35 technologies. The ABCA1 stabilizer exerts the efficacy of
ameliorating various diseases, such as low-HDL
cholesterolemia, which arise due to a decrease in the ABCA1

expression. In addition, since the stabilizer utilizes a metabolite of probucol which has been used as a drug, it is advantageous as a highly safe pharmaceutical drug. The present invention further provides an agent for increasing
5 the ABCA1 level and accelerating the HDL-generating reaction in vivo, increasing the blood level of HDL, enhancing the activity of blood cholesterol reverse-transport system which takes up cholesterol from peripheral tissues, and/or suppressing the degradation of ABCA1 and
10 accelerating the HDL-generating reaction in vivo, which contains at least one of the bisphenol compounds as an effective ingredient. The present invention further provides a method for prophylactic/therapeutic treatment of various diseases or abnormal conditions (specifically,
15 being associated with a decrease in the HDL blood level) which comprises administering at least one of the bisphenol-type compounds.

The above objects and other objects, features,
20 advantages, and aspects of the present invention are readily apparent to those skilled in the art from the following disclosures. It should be understood, however, that the description of the specification including the following best modes of carrying out the invention,
25 specific examples, etc. is illustrating preferred embodiments of the present invention and given only for illustrative purposes. It will become apparent to the skilled in the art that a great number of variations and/or alterations (or modifications) of this invention may be
30 made based on knowledge from the disclosure in the following parts and other parts of the specification without departing from the spirit and scope thereof as disclosed herein. All of the patent publications and reference documents cited herein for illustrative purposes
35 are hereby incorporated by reference into the present disclosure.

BEST MODES OF CARRYING OUT THE INVENTION

The present invention provides:

- 1) an ABCA1 stabilizer comprising an effective amount of at least one bisphenol-type compound selected from probucol spiroquinone, probucol diphenoxquinone, probucol bisphenol, and salts thereof;
- 5 2) a prophylactic/therapeutic agent for low-HDL cholesterolemia which comprises at least one ABCA1 stabilizer according to the above 1);
- 10 3) a prophylactic/therapeutic agent for arteriosclerosis which comprises at least one ABCA1 stabilizer according to the above 1); and
- 15 4) a drug comprising at least one member selected from the group consisting of ABCA1 stabilizers, prophylactic/therapeutic agents for low-HDL cholesterolemia, and prophylactic/therapeutic agents for arteriosclerosis, according to any of the above 1) to 3), in combination with at least one drug selected from the group consisting of
- 20 antidiabetes drugs, therapeutic drugs for complications of diabetes, antiobesity drugs, antihypertensive drugs, antihyperlipidemic drugs, diuretics, antithrombotic drugs, and anti-Alzheimer drugs.

25 The present invention further provides:

- 5) an agent for increasing the in vivo level of ABCA1 and accelerating the in vivo HDL-generating reaction which comprises an effective amount of at least one bisphenol-type compound selected from probucol spiroquinone,
- 30 probucol diphenoxquinone, probucol bisphenol, and salts thereof;
- 6) an agent for increasing the blood level of HDL which comprises an effective amount of said bisphenol compound;
- 35 7) an agent for increasing the activity of cholesterol reverse-transport that takes up, in blood, cholesterol from peripheral tissues, which comprises an

effective amount of said bisphenol-type compounds;

8) an agent for suppressing or inhibiting the in vivo degradation of ABCA1 and accelerating the in vivo HDL-generating reaction which comprises an effective amount of
5 said bisphenol-type compounds;

9) a prophylactic/therapeutic agent for low-HDL cholesterololemia which comprises an effective amount of at least one member selected from agents according to the above 5) to 8);

10 10) a prophylactic/therapeutic agent for arteriosclerosis which comprises an effective amount of at least one member selected from agents according to the above 5) to 8); and

11) a drug comprising an effective amount of at
15 least one member selected from agents according to the above 5) to 10), in combination with at least one drug selected from the group consisting of antidiabetes drugs, therapeutic drugs for complications of diabetes, antiobesity drugs, antihypertensive drugs,
20 antihyperlipidemic drugs, diuretics, antithrombotic drugs, and anti-Alzheimer drugs.

The present invention further provides:

a) a method for stabilizing ABCA1 which comprises
25 administering an effective dose of at least one bisphenol-type compound selected from probucol spiroquinone, probucol diphenoquinone, probucol bisphenol, and salts thereof to a subject;

b) a method for increasing the in vivo level of
30 ABCA1 and accelerating HDL-generation in vivo which comprises administering an effective dose of said bisphenol-type compounds to a subject;

c) a method for increasing the blood level of HDL which comprises administering an effective dose of said
35 bisphenol-type compounds to a subject;

d) a method for increasing the activity of cholesterol reverse-transport that takes up, in blood,

cholesterol from peripheral tissues, which comprises administering an effective dose of said bisphenol-type compounds to a subject;

5 e) a method for suppressing or inhibiting the degradation of ABCA1 and accelerating in vivo HDL-generation which comprises administering an effective dose of said bisphenol-type compounds to a subject;

10 f) a method for prophylactic/therapeutic treatment of low-HDL cholesterolemia which comprises administering an effective dose of at least one agent according to any of the above 1) and 5) to 8) to a subject;

15 g) a method for prophylactic/therapeutic treatment of arteriosclerosis which comprises administering an effective dose of at least one agent according to any of the above 1) and 5) to 8) to a subject; and

20 h) a method for prophylactic/therapeutic treatment of a disease which comprises administering an effective dose of at least one agent according to any of the above 1) to 3) and 5) to 10), in combination with an effective dose of at least one drug selected from the group consisting of antidiabetes drugs, therapeutic drugs for complications of diabetes, antiobesity drugs, antihypertensive drugs, antihyperlipidemic drugs, diuretics, antithrombotic drugs, and anti-Alzheimer drugs.

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The present invention provides A) a pharmaceutical drug containing, as an effective component, a bisphenol-type compound selected from probucol spiroquinone, probucol diphenoxquinone, probucol bisphenol, and salts thereof; and B) a pharmaceutical composition containing a pharmaceutically effective dose of a bisphenol-type compound selected from probucol spiroquinone, probucol diphenoxquinone, probucol bisphenol, and salts thereof, in admixture with a pharmaceutically acceptable excipient.

The above-mentioned probucol spiroquinone,

probucol diphenoquinone, and probucol bisphenol can be chemically synthesized by techniques, for example, disclosed in the Examples herein below. These compounds can be also isolated and purified by biochemical techniques
5 and chemical techniques, which are generally used, from in vivo metabolites produced when probucol is administered to a mammal.

Among the aforementioned bisphenol-type compounds,
10 when they are capable of forming salts, preferable salts thereof encompass pharmaceutically acceptable salts, including, for example, salts with inorganic or organic bases; salts with neutral, basic, or acidic amino acids; etc. Preferable examples of the inorganic bases include
15 alkaline metals such as sodium and potassium; alkali earth metals such as calcium and magnesium; aluminum; ammonium; etc. Preferable examples of the organic bases include trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,
20 dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Preferable examples of the neutral amino acids include glycine, valine, leucine, etc. Preferable examples of the basic amino acids include arginine, lysine, ornithine, etc. Preferable examples of the acidic amino acids include
25 aspartic acid, glutamic acid, etc.

The ABCA1 stabilizer is an agent or drug that provides the continuous and stable expression of ABCA1 mainly present in cell membranes of various organs such as
30 liver, small intestine, placenta, and adrenal gland. The stabilization of ABCA1 may refer to a state in which ABCA1 is being continuously and stably expressed. Examples of such a state may include, when ABCA1 levels are compared between in the presence and absence of the ABCA1 stabilizer,
35 a state in which ABCA1 is more continuously and stably present in cells (in particular, in cell membranes), a state in which ABCA1 is present in cells (in particular, in

cell membranes) so as to further accelerate the HDL-generating reaction, and a state in which ABCA1 is present in cells (in particular, in cell membranes) so as to further suppress or inhibit the degradation of ABCA1, under
5 the effect of the ABCA1 stabilizer.

The prophylactic/therapeutic agent for low-HDL cholesterolemia is a drug that prevents, relieves or cures low-HDL cholesterolemia. Low-HDL cholesterolemia is observed in diseases such as, in particular,
10 arteriosclerosis, hyperlipidemia, myocardial infarction, cerebral infarction, cerebral apoplexy, obesity, diabetes mellitus, nerve disorders caused by diabetes mellitus, thyroid dysfunction, hepatocirrhosis, myeloma, chronic renal failure, and chronic inflammatory bowel disease
15 (examples: Crohn's disease, chronic ulcerative colitis).
The prophylactic/therapeutic agent for low-HDL cholesterolemia comprising the ABCA1 stabilizer according to the present invention can be used for prophylactic/therapeutic treatment of any of the above-
20 mentioned diseases excepting genetic diseases, such as Tangier disease, in which ABCA1 is not normally synthesized
in vivo.

The prophylactic/therapeutic agent for
25 arteriosclerosis is a drug that prevents, relieves or cures arteriosclerosis. The ABCA1 stabilizer according to the present invention potently act in accelerating HDL-generation to increase blood HDL levels (or increase plasma HDL levels or serum HDL levels) as it will be clear from
30 Assay Examples herein below. The blood HDL plays an important role in the cholesterol reverse-transport system which prophylactically acts on arteriosclerosis. The drug of the present invention is also useful as a prophylactic/therapeutic agent for arteriosclerosis via the
35 action of increasing the blood HDL level.

In other words, in low-HDL cholesterolemia, the cholesterol reverse-transport system cannot sufficiently

work due to a decrease in the HDL level. Consequently, cholesterol accumulated in vascular walls is not readily transferred to the outside of the blood vessel, thereby resulting in acceleration of arteriosclerosis. Such a
5 condition can be ameliorated with the prophylactic/therapeutic agent for low-HDL cholesterolemia according to the present invention. Thus, the agent can be prophylactically and therapeutically applied to arteriosclerosis. Similarly, the bisphenol-type compounds
10 are useful for increasing the ABCA1 level and accelerating the HDL-generating reaction in vivo; increasing the blood level of HDL; increasing the cholesterol reverse-transport system activity in blood, which takes up cholesterol from peripheral tissues; and/or suppressing or inhibiting the
15 degradation of ABCA1 and accelerating the HDL-generating reaction in vivo. Therefore, the bisphenol compound can be used for prophylactic/therapeutic treatment of low-HDL cholesterolemia and arteriosclerosis.

20 In addition, the ABCA1 stabilizer of the present invention is useful for various diseases which are thought to be caused by a decrease in the ABCA1 expression, as follows:

Coronary artery disease (including cardiac
25 infarction, angina pectoris, asymptomatic myocardial ischemia, and coronary arteriosclerosis); atherosclerosis; carotid arteriosclerosis; cerebrovascular disease (including cerebral apoplexy and cerebral infarction); arteriosclerosis obliterans; fatty liver; hepatocirrhosis;
30 myeloma; diabetes mellitus; diabetic complication; dermatologic disease; xanthomatosis; arthritic disorder; proliferative disease; peripheral arterial obstruction; ischemic peripheral circulatory failure; obesity; cerebrotendinous xanthomatosis (CTX); chronic renal
35 failure; glomerular nephritis; arteriosclerotic nephritis; vascular thickening; vascular thickening after intervention (including percutaneous coronary plasty, percutaneous

coronary revascularization, detention of stent, coronary endoscopy, intravascular sonication, and percutaneous transluminal thrombolytic therapy); vascular reocclusion and restenosis after bypass operation; nephropathy,
5 nephritis, and pancreatitis, which highly relate to hyperlipidemia; hyperlipidemia (including familial hypercholesterolemia and postprandial hyperlipidemia); chronic inflammatory bowel disease (including Crohn's disease and chronic ulcerative colitis); intermittent
10 claudication; deep venous thrombosis; malaria encephalitis; Alzheimer's disease; and diseases accompanied with wound or ateliosis.

The drug containing the active ingredient according to the present invention is effective for prophylactic/therapeutic treatment of various diseases or abnormal conditions which are associated with a decrease in the blood HDL level, and is obviously useful for the above-mentioned diseases.

The ABCA1 stabilizer, prophylactic/therapeutic agent for low-HDL cholesterolemia, and prophylactic/therapeutic agent for arteriosclerosis according to the present invention may be administered alone or in combination with other drugs described below, preferably in a form of a drug containing a pharmaceutically acceptable excipient. The agent is administered by an oral route or injection. In addition, the drug may be in topical form (such as percutaneous drug or ointment), suppository form (such as rectal suppository and vaginal suppository), pellet form, nasal-drop form, inhalant form (such as a form using a nebulizer), or eye-drops form. In any administration route of the drug, a component (hereinafter sometimes referred to as "pharmaceutical component") selected from known pharmaceutical excipients can be optionally used.
30 Specifically, examples of known excipients are disclosed in, for example, (1) Iyakuhin Tenkabutsu Handobukku (Handbook of Pharmaceutical Excipients), MARUZEN, 1989, (2) Iyakuhin
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Tenkabutu Jiten (Encyclopedia of Pharmaceutical Excipients),
1st Edition, Yakuji Nippo, 1994, (3) Iyakuhin Tenkabutsu
Jiten Tsuiho (Encyclopedia of Pharmaceutical Excipients,
Supplement), 1st Edition, Yakuji Nippo, 1995, and (4)
5 Yakuzaigaku (Pharmacology), Revised 5th Edition, Nankodo,
1997. The pharmaceutical component may be optionally
selected from the known pharmaceutical excipients shown
above depending on the administration route and application
purpose of the drug. Similarly, the agent of the present
10 invention for increasing the ABCA1 level and accelerating
the HDL-generating reaction in vivo; increasing the blood
level of HDL; increasing activity of the cholesterol
reverse-transport system in blood, which removes
cholesterol from peripheral tissues; and/or suppressing the
15 degradation of ABCA1 and accelerating the HDL-generating
reaction in vivo may be administered as described above.

For example, when the drug is administered orally,
any excipient can be used as long as the excipient can
20 constitute an oral drug as a pharmaceutical component and
achieve purposes of the present invention. Generally, the
excipient is selected from known pharmaceutical components
including for example fillers, binders, disintegrants,
lubricants, and coating agents (including taste masking
25 agents). Examples of the oral drug include tablets
(including sublingual tablets and orally disintegrating
tablets), capsules (including soft capsules and
microcapsules), granules, fine granules, powders, troches,
and syrups. The oral drugs include those (examples: rapid-
30 release drugs and sustained-release drugs) in which a known
pharmaceutical component is used to control the in vivo
release of an active component (i.e., an effective
ingredient), i.e., the in vivo release of probucol
spiroquinone, probucol diphenoquinone, or probucol
35 bisphenol.

When the drugs are administered by injection

routes, the excipient used includes any pharmaceutical component which can constitute an aqueous injection or non-aqueous injection. In general, known pharmaceutical components which are used include dissolving agents,
5 dissolving aids, suspending agents, isotonizing agents, buffering agents, stabilizing agents, preservatives, etc. In addition, the excipient used may include known pharmaceutical compounds which constitute powder injections. The powder injections are used after being dissolved or
10 suspended when they are administered. Examples of the pharmaceutical components for aqueous injections include distilled water for injection and sterile isotonic salt solutions (containing, for example, monosodium phosphate, disodium phosphate, sodium chloride, potassium chloride,
15 calcium chloride, magnesium chloride, or a mixture thereof). Examples of the pharmaceutical components for non-aqueous injections include vegetable oils such as olive oil, sesame oil, cotton oil, and corn oil; propylene glycol; macrogol; and tricapryline. The drugs are prepared by dissolving,
20 suspending, or emulsifying the active component in these pharmaceutical components. Examples of the injections include subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, and intravenous drips. Provided thus is use of the bisphenol-type compounds for preparing drugs (pharmaceutical drugs or
25 pharmaceutical compositions) which contain the active ingredient or active component of the present invention and have the above-mentioned activities.

30 The effective dose of the ABCA1 stabilizer, prophylactic/therapeutic agent for low-HDL cholesterolemia, and prophylactic/therapeutic agent for arteriosclerosis according to the present invention varies and is optionally controlled depending on the age and weight of a subject,
35 symptoms of the low-HDL cholesterolemia or arteriosclerosis, and the presence or absence of complications. In general, the dose is about 0.1 to 3000 mg/day when the agent is

administered orally, and the dose is about 0.1 to 1000 mg/day when the agent is administered by injection.

Similarly, the agent of the present invention for increasing the ABCA1 level and accelerating the in vivo

5 HDL-generating reaction; increasing the blood level of HDL; activating or stimulating the cholesterol reverse transport pathway in blood, which removes cholesterol from peripheral tissues; and/or suppressing the degradation of ABCA1 and accelerating the in vivo HDL-formation may be administered
10 as described above.

The ABCA1 stabilizer, prophylactic/therapeutic agent for low-HDL cholesterolemia, and

prophylactic/therapeutic agent for arteriosclerosis according to the present invention can be used as a

15 combination with one or more other drugs, which do not adversely affect actions of the inventive agents, in order to increase the efficacy, reduce the dose to be administered, and decrease side-effects. The drug used in the combination may include low molecular-weight compounds,
20 polypeptides, antibodies, vaccines, etc. Such drugs include, for example, "antidiabetes drugs", "therapeutic drugs for complications of diabetes", "antiobesity drugs", "antihypertensive drugs", "antihyperlipidemic drugs", "diuretics", "antithrombotic drugs", "anti-Alzheimer drugs",
25 and others. Similarly, the agent of the present invention for elevating the ABCA1 level and accelerating the HDL formation in vivo; increasing the blood level of HDL; activating the cholesterol reverse-transport pathway in blood, which removes cholesterol from peripheral tissues;
30 and/or inhibiting the degradation of ABCA1 and accelerating the HDL formation in vivo may be administered as described above.

The "antidiabetes drug" includes, for example,

35 insulin secretagogues, biguanides, insulin, and α -glucosidase inhibitors. The insulin secretagogue includes, for example, tolbutamide, chlorbutamide, chlorpropamide,

tolazamide, acetohexamide, glyclopypamide, glibenclamide,
gliclazide, glibuzol, glimepirid, nateglinide, and
mitiglinide. The biguanide includes, for example,
phenformin, metformin, and buformin. The α -glucosidase
5 inhibitor includes, for example, acarbose, voglibose,
miglitol, and emiglitol.

The "therapeutic drug for complications of
diabetes" includes, for example, aldose-reductase
inhibitors such as epalrestat, alprostadil, and mexiletine
10 hydrochloride.

The "antiobesity drug" includes, for example,
lipase inhibitors and appetite suppressants. The lipase
inhibitor includes, for example, orlistat. The appetite
15 suppressant includes, for example, dexfenfluramine,
fluoxetine, sibutramine, and baiamine.

The "antihypertensive drug" includes, for example,
angiotensin-converting enzyme inhibitors, calcium
20 antagonists, and angiotensin II antagonists. The
angiotensin-converting enzyme inhibitor includes, for
example, captopril, enalapril, alacepril, delapril,
lisinopril, imidapril, benazepril, cilazapril, perindopril,
quinapril, temocapril, trandolapril, and manidipine. The
25 calcium antagonist includes, for example, nifedipine,
amlodipine, efonidipine, and nicardipine. The anigotensin
II antagonist includes, for example, losarutan, cardesartan
cilexetil, valsartan, and irbesartan.

30 The "antihyperlipidemic drug" includes, for
example, HMG-CoA reductase inhibitors and fibrates. The
HMG-CoA reductase inhibitor includes, for example, statins
such as pravastatin, simvastatin, lovastatin, atorvastatin,
and fluvastatin. The fibrates include, for example,
35 bezafibrate, clinofibrate, clofibrate, fenofibrate, and
simfibrate. In addition to the above-mentioned drugs, the
"antihyperlipidemic drug" includes, for example, anion

exchange resins (example: cholestyramine), nicotinic acid agents (examples: nicomol and nericitrol), and ethyl icosapentate.

5 The "diuretic" includes, for example, thiazide drugs such as cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penfluthizide, and methyclothiazide. In addition to the above-mentioned drugs,
10 the diuretic includes isosorbide and furosemide.

15 The "antithrombotic drug" includes, for example, heparin, warfarin, antithrombin agents, thrombolytic agents, and platelet-aggregation-suppressing agents (anti-platelet agents).

The "anti-Alzheimer drug" includes, for example, donepezil, rivastigmine, and galantamine.

When the ABCA1 stabilizer,
20 prophylactic/therapeutic agent for low-HDL cholesterolemia, or prophylactic/therapeutic agent for arteriosclerosis according to the present invention is applied in combination with any of the concomitant agents, the dosage form is not specifically limited as long as the agent of
25 the present invention is coadministered with the concomitant agent. Examples of such dosage forms include those for administrating a single dosage unit prepared by formulating the agent of the present invention and the concomitant agent together; for administrating two kinds of
30 drugs at the same time or at an interval via identical routes, wherein the two kinds of drugs are prepared by separately formulating the agent of the present invention and the concomitant agent; and for administrating two kinds of drugs at the same time or at an interval via different
35 routes, wherein the two kinds of drugs are prepared by separately formulating the agent of the present invention and the concomitant agent.

The present invention provides a method for prophylactic/therapeutic treatment of diseases with the bisphenol-type compounds. For example, the method for prophylactic/therapeutic treatment of diseases can be 5 performed by administering an effective dose of the bisphenol-type compounds to a subject or target. The inventive method for prophylactic/therapeutic treatment of diseases may be performed while monitoring conditions and symptoms of a subject. The monitoring may be conducted at 10 regular or irregular intervals of time, or may be periodically conducted. Typically, the method is performed while monitoring the blood HDL level. The drugs of the present invention may be administered at regular or irregular intervals of time, or may be periodically 15 administered.

The term "prophylactic/therapeutic treatment" used herein refers to preventive treatment and/or curative treatment, i.e., including (1) prophylactic and therapeutic treatments, and (2) prophylactic treatment or therapeutic 20 treatment.

Examples, etc.

Details of the present invention are described by the following examples including Synthesis Examples, Assay Examples, and Formulation Examples, but such examples are provided only for illustrative purposes, and for referential embodiments of the present invention. These examples should in no way be construed as limiting and restricting the scope of the invention disclosed herein.

It should be understood in the present invention that various embodiments can be made or executed within the spirit, scope and concept disclosed herein.

All the Assay Examples and other Examples were performed or can be performed, unless otherwise disclosed herein specifically, according to standardized techniques which are well-known and conventional to those skilled in the art. In Examples herein below, specific processes and treatment conditions were performed, unless specific indication is provided, according to attached protocols with attached reagents when commercially available reagents or kits were used.

25 Synthesis Example 1
 Synthesis of probucol spiroquinone

A mixture of probucol (981 mg, 1.9 mmol: Wako Pure Chemical Industries, Ltd.) and lead oxide (4.04 g) in dichloromethane (20 mL) was stirred overnight. The mixture was filtered, evaporated, then washed with methanol, and dried to yield a crystal, probucol spiroquinone (912 mg, 93%). Chemical ionization mass spectra (CI-MS) were recorded on a double-focusing magnetic sector mass spectrometer (MS700: JEOL). Elemental analysis was conducted with a CHN autoanalyzer (Vario EL: Elementar).

mp 156-158°C

¹H NMR (CDCl₃) δ: 1.20 (36H, s), 2.01 (6H, s), 6.88 (4H, s)
CI(positive)-MS (m/z): 515 (M+1), 473 (M-C₃H₆), 441 (M-C₃H₆S+1), 409 (M-C₃H₆S₂+1, diphenoxquinone+1), 279 (M-

5 C₁₄H₂₀OS+1), 237 (C₁₄H₂₀OS+1)

Anal. calcd. for C₃₁H₄₆O₂S₂: C, 72.32; H, 9.01. Found: C, 72.3; H, 9.0

10

Synthesis Example 2

Synthesis of probucol diphenoxquinone

A methanol solution (100 mL) of 2,6-di-t-butylphenol (309 mg, 1.5 mmol) was oxidized under the presence of phthalocyanine-Fe (II) (853 mg, 1.5 mmol) at a room temperature for 5 hours according to a method of Tada, et al. [Bull. Chem. Soc., 45, 2558-2559, (1972)]. The resultant reaction mixture was stirred until the reaction was completed, and then evaporated. The resulting residue was dissolved in ethanol, filtered, and evaporated to yield a crystal, probucol diphenoxquinone (340 mg, 100%).

Electron impact mass spectra (EI-MS) were recorded on a double-focusing mass spectrometer (AX505W: JEOL).

mp 223-225°C

25 ¹H NMR (CDCl₃) δ: 1.37 (36H, s), 7.71 (4H, s)

EI-MS (m/z): 408 (M), 393 (M-CH₃), 351 (M-C₄H₉)

Synthesis Example 3

Synthesis of probucol bisphenol

To a solution of probucol diphenoxquinone (349 mg, 0.86 mmol), prepared in Synthesis Example 2, in methanol (20 mL) and dichloromethane (20 mL) was added sodium

35 borohydride (72 mg, 1.88 mmol) under nitrogen atmosphere. The resultant reaction mixture was stirred for 1 hour, evaporated, then washed with water, and dried to yield a

crystal, probucol bisphenol (244 mg, 70%). Electron impact mass spectra (EI-MS) were recorded on a double-focusing mass spectrometer (AX505W: JEOL).

mp 184-186°C

5 ^1H NMR (CDCl_3) δ : 1.49 (36H, s), 5.18 (2H, s), 7.30 (4H, s)
EI-MS (m/z): 410 (M), 395 (M- CH_3)

Assay Example 1

10 Increase in the ABCA1 expression by probucol spiroquinone, probucol diphenoxquinone, and probucol bisphenol in THP-1 cells

<Assay method>

15 THP-1 cells (human leukemia cells: American Type Culture Collection) were cultured for 72 hours in a 10% FBS-RPMI1640 medium (Iwaki Glass Co., Ltd.) under the presence of PMA (phorbol myristate acetate, 3.2×10^{-7} M: Wako Pure Chemical Industries, Ltd.) to obtain
20 differentiated macrophages. Probucol spiroquinone (Synthesis Example 1), probucol diphenoxquinone (Synthesis Example 2), or probucol bisphenol (Synthesis Example 3) was added to a medium after being incorporated into acetyl-LDL according to a method of Tsujita, et al. [BIOCHEMISTRY, 35, 25 13011-13020 (1996)]. The cells were cultured in this medium for 48 hours, and then further cultured for 24 hours in the presence or absence of apoAI. The expression levels of intracellular ABCA1 were assayed according to a method disclosed herein below.

30 The agent-treated cells and non-treated cells were hypotonically disrupted in 5 mM Tris-HCl (pH 8.5), and then centrifuged (650 g for 5 minutes) to precipitate nuclear fractions. The supernatant was centrifuged at 105,000 g for 30 minutes to collect a total membrane fraction. The total membrane was dissolved in a solution containing 0.9 M urea, 0.2% Triton X-100, and 0.1% dithiothreitol, followed by addition of 10% lithium dodecyl
35

sulfate solution at a volume ratio of 1/4. The resultant was subjected to electrophoretic separation using 10% SDS-7% polyacrylamide gel. The separated proteins were transferred and fixed onto PVDF membrane (Bio-Rad), and
5 then subjected to immunoblotting with anti-human ABCA1 rabbit antibody (self-purified by an ordinary technique) to examine expressed ABCA1 protein levels. The obtained bands of the protein were read for density and size with Scion Image (image analysis software: Scion) to convert the
10 results into digitized forms. The relative ratio of the ABCA1 expression level of the drug-treated cells to that of the non-treated cells was calculated to evaluate the ABCA1-expression activity of the assayed compounds. The results are shown in Table 1.

15

<Results>

As shown in Table 1, it was observed that the intracellular ABCA1 expression levels of the THP-1 cells treated with probucol spiroquinone, probucol diphenoxquinone,
20 or probucol bisphenol were remarkably elevated, as compared with that of the non-treated cells.

Table 1

Assayed Compound	ABCA1 Expression Level (Relative Ratio %)
Control (Non-treated)	100
Probucol spiroquinone	191
Probucol diphenoxquinone	173
Probucol bisphenol	153

Assay Example 2

Acceleration of HDL-generating reaction by probucol
spiroquinone, probucol diphenoxquinone, and probucol
bisphenol

5

<Assay method>

The cultured cells obtained in the same manner as in Assay Example 1 were examined for cholesterol and phospholipid taken out into the medium by the apoAI-dependent HDL-generating reaction, according to a method of Arakawa, et al. [J. LIPID RES., 41, 1952-1962, (2000)]. The results of the drug-treated cells were compared with that of non-treated cells (control). The resulting data were converted into digitized forms as in Assay Example 1, and the relative ratios of the taken out level in the drug-treated cells to that in the non-treated cells were calculated to evaluate the HDL-generating reaction accelerated by the assayed compounds. The results are shown in Table 2. For comparison, the HDL-generating reaction accelerated by probucol (Wako Pure Chemical Industries, Ltd.) was examined in the same manner as aforementioned.

<Results>

As shown in Table 2, it was observed that the levels of apoAI-dependently taken out HDL cholesterol were about 1.3 to 1.6 times elevated in the THP-1 cells treated with probucol spiroquinone, probucol diphenoxquinone, or probucol bisphenol, as compared with that of the non-treated cells. Similarly, the levels of apoAI-dependently taken out phospholipid were also about 1.4 to 2.0 times increased in the THP-1 cells treated with probucol spiroquinone, probucol diphenoxquinone, or probucol bisphenol, as compared with that of the non-treated cells. On the other hand, in the THP-1 cells treated with probucol, no apoAI-dependently taken out HDL cholesterol was observed and the level of taken out phospholipid was decreased to

less than 1/3, as compared with that of the non-treated cells.

Table 2

Assayed Compound	Release of HDL Cholesterol (Relative Ratio %)	Release of Phospholipid (Relative Ratio %)
Control (Non-treated)	100	100
Probucol spiroquinone	148	151
Probucol diphenoquinone	159	200
Probucol bisphenol	137	144
Probucol	0	34

5

Assay Example 3

Increase of blood HDL level by probucol spiroquinone and

10 probucol diphenoquinone (mouse)

<Assay method>

Probucol spiroquinone (Synthesis Example 1: 50 mg/kg or 150 mg/kg) or probucol diphenoquinone (Synthesis Example 2: 50 mg/kg or 150 mg/kg) suspended in a 0.5% carboxymethylcellulose solution was orally administered to each group of 3 or 4 mice once a day for 7 days. To a control group, only the 0.5% carboxymethylcellulose solution was administered in the same manner. Animals were subjected to laparotomy under ether anesthesia at 3 hours after the last administration, and blood was collected in the presence of heparin sodium from the heart of each mouse. The blood was centrifuged at 2000 g for 10 minutes to separate plasma. The plasma was applied to electrophoresis using Paragon Electrophoresis System (Beckman Coulter, Inc.) to separate plasma lipoprotein, followed by lipid staining. The images on the gel after the lipid staining were examined to convert the plasma HDL level of each mouse

15

20

25

into a digitized form for the evaluation.

<Results>

5 As shown in Table 3, it was observed that the plasma HDL levels in mice administered with test drugs were increased about 1.2 times for probucol spiroquinone and about 1.1 to 1.8 times for probucol diphenoxquinone, respectively, compared with that in control group.

10

Table 3

Assayed Compound	Plasma HDL Level (Relative Ratio %)	
	50 mg/kg	150 mg/kg
Control (Non-treated)	100	100
Probucol spiroquinone	120	124
Probucol diphenoxquinone	113	180

15

Assay Example 4

Increase of blood HDL level by probucol spiroquinone, probucol diphenoxquinone, and probucol bisphenol (rabbit)

<Assay method>

20 Microemulsions were prepared by adding probucol spiroquinone (Synthesis Example 1), probucol diphenoxquinone (Synthesis Example 2), or probucol bisphenol to a mixture of triolein (Sigma Chemical Co.) and phosphatidyl choline (Avanti Polar Lipids). The microemulsion (0.5 to 10 mL/body) was administered to each group of 4 rabbits via the ear vein once a day for 7 days. To a control group, a microemulsion containing no test drug was administered in the same manner. Blood was collected in the presence of heparin sodium from the ear vein of each rabbit at 3 hours
25 after the last administration. The blood was centrifuged
30

at 2000 g for 10 minutes to separate plasma. The plasma was applied to electrophoresis using Paragon Electrophoresis System (Beckman Coulter, Inc.) to separate plasma lipoprotein, followed by lipid staining. The images 5 on the gel after the lipid staining were examined to convert the plasma HDL level of each rabbit into a digitized form for the evaluation. In reference to the content amount of each compound in the microemulsion, each blood compound level assumed just after the intravenous administration 10 thereof was set as the dose of each compound.

<Results>

As shown in Table 4, it was observed that the plasma HDL levels in rabbits administered with test drugs 15 were increased about 1.5 to 1.9 times for probucol spiroquinone, about 1.3 to 1.4 times for probucol diphenoquinone, and about 1.3 to 1.4 times for probucol bisphenol, respectively, compared with that in control group.

20

Table 4

Assayed Compound	Plasma HDL Level (Relative Ratio %) (Blood Level: μM)	
Control (Non-treated)	100	
Probucol spiroquinone	157 (0.14)	194 (0.57)
Probucol diphenoquinone	148 (0.16)	130 (0.31)
Probucol bisphenol	145 (0.14)	135 (0.57)

25

Assay Example 5

Toxicity Test

Probucol spiroquinone, probucol diphenoquinone, and probucol bisphenol were orally administered to mice for 30 one week. As a result, it was verified that no abnormal

findings were observed.

As shown above, it was confirmed that the ABCA1 stabilizer of the present invention provides the continuous 5 and stable expression of ABCA1 without using genetic engineering techniques and accelerates the HDL-generating reaction, thereby acting as a prophylactic/therapeutic agent for low-HDL cholesterolemia. The active ingredients, the bisphenol-type compounds, according to the present 10 invention have activity of elevating blood HDL levels, and hence are expected to have activity of modifying the cholesterol reverse-transport system to a preferable direction.

15

Formulation Example 1

According to the present invention, probucol 20 spiroquinone: 200 mg, lactose: 100 mg, corn starch: 28 mg, and magnesium stearate: 2 mg

The ingredients of the prescription above were formulated into capsules according to a known method specified in The Japanese Pharmacopoeia XIV, General Rules 25 for Preparations.

Formulation Example 2

According to the present invention, probucol 30 spiroquinone (25 mg) was dissolved in an aqueous isotonic solution of distilled water for injection (10 mL) containing an appropriate amount of sodium chloride. The resulting mixture was dispensed in each ampule, and then 35 subjected to sterilization after sealing to obtain injections.

INDUSTRIAL APPLICABILITY

The ABCA1 stabilizers each containing an effective amount of a bisphenol-type compound selected from 5 probucol spiroquinone, probucol diphenoxquinone, and probucol bisphenol according to the present invention give the continuous and stable expression of ABCA1 without using complicated genetic engineering techniques. The ABCA1 stabilizers are effective drugs for various diseases such 10 as low-HDL cholesterolemia and arteriosclerosis caused by a decrease in the ABCA1 expression. In addition, the ABCA1 stabilizers of the present invention utilize a metabolite of probucol which has already been assured to be pharmaceutically safe, and thus are useful as drugs because 15 of their safety. Similarly, the effective ingredients can be used as agents for increasing the ABCA1 level and accelerating the HDL-generating reaction in vivo; increasing the blood level of HDL; activating the blood cholesterol reverse-transport pathway which takes up 20 cholesterol from peripheral tissues; and/or suppressing the degradation of ABCA1 and accelerating in vivo HDL formation, and further can be used for prophylactic/preventive treatment of various diseases or abnormal conditions (specifically, being associated with a decrease in the 25 blood HDL level).

While the present invention has been described specifically in detail with reference to certain embodiments and examples thereof, it would be apparent that 30 it is possible to practice it in other forms. In light of the disclosure, it will be understood that various modifications and variations are within the spirit and scope of the appended claims.